This report is required by law (7 USC 2143). Failure to report according to the regulations can result in an order to cease and desist and to be subject to penalties as provided for in Section 2150.

See reverse side for additional information.

Interagency Report Control No 0180-DOA-AN

UNITED STATES DEPARTMENT OF AGRICULTURE
ANIMAL AND PLANT HEALTH INSPECTION SERVICE

ANNUAL REPORT OF RESEARCH FACILITY
(TYPE OR PRINT)

1. REGISTRATION NO. 57-R-0118 **CUSTOMER NO.** 16294

FORM APPROVED
OMB NO. 0579-0036

2. HEADQUARTERS RESEARCH FACILITY *(Name and Address, as registered with USDA, include Zip Code)*

INHIBITEX INC
9005 WESTSIDE PKWY
ALPHARETTA, GA 30004
(678) 746-1100

3. REPORTING FACILITY (List all locations where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes. Attach additional sheets if necessary.)

See Attached Listing

(b)(2)High, (b)(7)(F)

CATIONS*(sites)*

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BY:

REPORT OF ANIMALS USED BY OR UNDER CONTROL OF RESEARCH FACILITY *(Attach additional sheets if necessary or use APHIS FORM 7023A)*

A. Animals Covered By The Animal Welfare Regulations	B. Number of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.	C. Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs.	D. Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used.	E. Number of animals upon which teaching, experiments, research, surgery or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic,analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. *(An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report)*	F. TOTAL NO. OF ANIMALS (Cols. C + D + E)
4. Dogs					
5. Cats					
6. Guinea Pigs					
7. Hamsters					
8. Rabbits			7	83	90
9. Non-Human Primates					
10. Sheep					
11. Pigs					
12. Other Farm Animals					
13. Other Animals					

ASSURANCE STATEMENTS

1) Professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by this research facility.

2) Each principal investigator has considered alternatives to painful procedures.

3) This facility is adhering to the standards and regulations under the Act, and it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the Institutional Animal Care and Use Committee (IACUC). **A summary of all the exceptions is attached to this annual report.** In addition to identifying the IACUC-approved exceptions, this summary includes a brief explanation of the exceptions, as well as the species and number of animals affected.

4) The attending veterinarian for this research facility has appropriate authority to ensure the provision of adequate veterinary care and to oversee the adequacy of other aspects of animal care and use.

CERTIFICATION BY HEADQUARTERS RESEARCH FACILITY OFFICIAL
(Chief Executive Officer or Legally Responsible Institutional official)

certify that the above is true, correct, and complete (7 U.S.C. Section 2143)

FICIAL NAME & TITLE OF C.E.O. OR INSTITUTIONAL

(b)(6),(b)(7)(c)

(b)(6),(b)(7)(c)

DATE SIGNED 11/10/06

18-23 (Oct 88), wl

ART 1 - HEADQUARTERS

Column E Explanation

1. **Registration Number: 57-R-0118 / 16294**

2. **Number of animals (in category E) used in this study: 83**

3. **Species (common name) of animals used: Rabbit**

4. **Explain the procedure producing pain and/or distress:**

The studies described here are to evaluate new therapeutic agents for the treatment of life threatening infections with Staphylococcus or Enterococcus bacteria. A standard model, the Rabbit Infective Endocarditis Model, is used for these evaluations. Rabbits are provided appropriate anesthesia for surgical placement of catheters but are not given analgesic drugs following infection with bacteria.

Rabbits undergo general surgical anesthesia by administration of the anesthetic combination of Ketamine/Xylazine and Butorphanol along with infiltration of the incision site with the Lidocaine. A carotid artery-to-left ventricle catheterization is performed. Subsequently, *Staphylococcus aureus*, *Enterococcus faecalis*, or *Enterococcus faecium* mediated infectious endocarditis is induced by intravascular injection of these bacteria.

Treatment groups receive the test treatment compound or control vehicle approximately 48 to 72 hours following catheterization. Bacterial challenge occurs approximately 24 hours following treatment administration.

Study length is then 72 to 96 hours post-bacterial challenge. Following bacterial challenge the animals are observed for evidence of illness a minimum of twice daily. Some animals develop extensive infection. Infected animals most often have reduced food and water consumption and severely decreased activity. Animals exhibiting such behavior are immediately euthanized. Treatment efficacy is determined by the bacterial burden per gram of tissue. Early termination of animals with extensive infection is imperative for the analysis of the treatments.

5. **Provide scientific justification why pain and/or distress could not be relieved. State methods or means used to determine that pain and/or distress relief would interfere with test results:**

The infectious disease model described in section 4 relies on a normally functioning immune system to evaluate the effectiveness of potential therapeutic antibodies engineered to promote bacterial clearance. Once the bacterial challenge is initiated, no further analgesics are administered due to their potential to alter the normal anti-microbial immune response. Analgesics such as non-steroidal anti-inflammatory

drugs (NSAIDS) were developed to suppress the inflammatory response through the inhibition of cyclooxygenase. However, NSAIDS have also been shown to have effects on cytokine production[1], lymphocyte response[2] and neutrophil function[3]. Alternatively, opiate derived analgesics could be used, however, there is clear evidence that opiate derived analgesics have immunomodulatory effects both in animal models and in humans[4]. For these reasons, it is established practice to avoid the use of analgesics in *in vivo* models of immune function[5]. The use of post-operative analgesics in this model would interfere with our ability to interpret experimental results when using immune based therapies.

[1] Ertel, W., M. H. Morrison, D. R. Meldrum, A. Ayala and I. H Chaudry. 1992. Ibuprofen restores cellular immunity and decreases susceptibility to sepsis following hemorrhage. J. Surg. Res. 53(1): 55-61.

[2] Rossi Paccani, S., M. Boncristiano and C. T. Baldari. 2003. Molecular Mechanisms underlying suppression of lymphocyte responses by nonsteroidal anti-inflammatory drugs. Cell Mol. Life Sci. 60(6):1071-1083.

[3] Kang, K., S. J. Bae, W. M. Kim, D. H. Lee, U. Cho, M. H. Lee, M. S. Lee, S. Nam, K. E. Kuettner and D. E. Schwartz. 2000. Molecular characteristics of the inhibition of human neutrophil elastase by nonsteroidal anti-inflammatory drugs.

[4] Bryant, H. U. & J. W. Holoday. 1993. in *Opioids in Immunologic Processes*, ed. A Herz (Springer Berlin) Vol. 104/II, pp. 361-335.

[5] Piersma, F. E., M. A. Daemen, A. E. Bogaard, W. A. Buurman. 1999. Interference of pain control employing opioids in *in vivo* immunological experiments. Lab Anim. 33(4):328-333.

6. **What, if any federal regulations require this procedure?** No federal regulations require this procedure.